DRUG INFORMATION ASSOCIATION

FDA/DIA SCIENTIFIC WORKSHOP ON FOLLOW-ON PROTEIN PHARMACEUTICALS

BREAKOUT SESSION F

CLINICAL SAFETY AND EFFICACY STUDIES

Tuesday, February 15, 2005

1:33 p.m.

Marriott Crystal Gateway
1700 Jefferson Davis Highway
Arlington, Virginia

PARTICIPANTS

MODERATORS:

DAVID ORLOFF, MD, FDA/CDER

MARC WALTON, FDA/CBER

DOROTHY SCOTT, MD, FDA/CBER

DAWN VIVEASH

YAFIT STARK, Ph.D

P R O C E E D I N G S

DR. ORLOFF: I think we are ready to start, folks. It looks like we have a reasonable crowd. Hopefully, people are primed to discuss--this is the breakout session for approaches to clinical and safety efficacy studies.

Again, I am David Orloff. My panelists include Dr. Mark Walton, Dr. Dorothy Scott, Dr. Dawn Viveash, on my immediate left, and Dr. Yafit Stark, all the way on the end.

We are going to begin with two presentations, from Dr. Stark first and then from Dr. Viveash, and then we will raise the questions, which I guess I could probably just throw up on the screen for now, which will at least form the basis for the initial part of our discussion.

I think the rules of this are going to be two presentations, save your questions and comments. In the discussion session, we will try our best to focus on one question at a time. When the conversation lags or when the tangential questions get too irritating, we will move on to

the next question, tangential comments.

Let me call Dr. Stark to the lectern here. Yafit Stark, Ph.D., is Senior Director, Global Clinical Research at TEVA Pharmaceuticals Industries, Limited. Please.

DR. STARK: Thank you, David. I would like to thank the organizers for inviting me all the way to come from Tel Aviv to Arlington. It is a pleasure.

It is also a pleasure to have two hats. One is I am working in the last 18 years in the innovative R&D, trying to develop innovative products for the treatment of autoimmune diseases and CNS indications and other indications, but, on the same token, to represent TEVA Sicor in the biologic generic clinical development.

So thanks again for inviting me here. I would like, also, to thank the two presenters in the plenary session, Dr. Siegel and Dr. Carole Ben-Maimon, for setting the stage for our talk today.

Now, David, what shall I do next?

DR. ORLOFF: I'm sorry. Just read the questions.

DR. STARK: Most of the breakout sessions

that I attended, the major issue that we are facing currently while we are developing biopharmaceutical generics is how to minimize the risks for the patients.

Actually, we are trying to develop comparable products. The biopharmaceutical generics are aiming at developing comparable products to the innovator.

The question that we should ask ourselves is when clinical studies are to be--when should we do clinical studies. When we are talking about clinical studies, we are not aiming right now to discuss the pharmacokinetics and pharmacodynamics, which was discussed in a separate breakout session.

I am trying to summarize what was discussed this morning by our two colleagues, Dr. Siegel and Dr. Ben-Maimon. Our belief is that in very rare cases, clinical studies will be necessary, but the question that we should ask

ourselves is when should we conduct such clinical studies.

It may very well be that when uncertainties as to the comparability remain after the analytical or the biological characterization, maybe following, also, animal pharmacokinetic and pharmacodynamic studies, if there are still uncertainties under our goal to minimize the risk to the patient, we should conduct clinical studies.

Now, if we are trying to design our clinical development for our biopharmaceutical generic, the question is to what extent, what should be our clinical development plan, how many questions should we answer during our clinical development plan.

In general, we know that there is extensive clinical information and experience accumulated over the years by the innovator during its development and since the innovator product was put into the market.

Of course, we can use this information and sometimes it's the best information, clinical

studies may be unwarranted, but, again, it has to be judged on a case by case basis.

We should have to look at the clinical information about the innovator, about the drug class, and about the indications.

As was previously discussed, when clinical studies are to be done, we should also utilize surrogate markers, if they are available. Sometimes surrogate markers have been developed during the clinical development. Sometimes they are validated during the marketing phase.

So in utilizing surrogate markers or now the mainstay for clinical studies not only for biopharmaceutical generics, but I am hearing in other FDA sessions that in the future, we will rely, also, on an innovator's development to utilize surrogate markers in confirmatory studies.

But, again, when surrogate markers are not validated or do not exist, we may go to a clinical outcome measure. Again, we have to do targeted clinical studies, as discussed previously, aiming at specific questions that will be clinically and

scientifically sound.

Safety should be our major goal. Again, our safety profile that it's comparable to that of the brand can be also assured through the characterization, as well as animal studies, pharmacokinetics and/or pharmacodynamics.

In the case of uncertainties or questions that still remain following all these studies, first, we may run clinical studies, and, in case we do clinical studies, of course, we will follow the safety of the patient toward the clinical studies.

Again, as all other products, safety of the protein products will be closely monitored during the clinical development, if clinical studies are to be conducted, as well as in the market, and, of course, by putting a very active pharmacovigilance program.

By that, we will be able to expose more patients and to be able to detect subtle differences that sometimes clinical studies with a limited number of patients are not able to do.

So by this, I have summarized, in general,

when clinical studies should be done, what should be, in general, the design of the clinical studies, and how closely should we monitor safety.

DR. ORLOFF: Thank you, Dr. Stark. The next speaker is Dawn Viveash. She is Vice President-Regulatory Affairs, from Amgen, Incorporated. Let me get your talk up here, Dawn. There you go.

DR. VIVEASH: Thank you. It is a great pleasure to be here today. A lot of stimulating discussion, and I am really honored to be part of this particular session. I think we are going to have a lot of good debate here.

For those of you who are in need of a post-prandial snooze, that is okay. One request I have, if you are going to snooze, just try to think back on the discussions this morning, because the points I am going to make I think primarily were covered this morning.

I am going to try to give a few highlights in three slides. So that's kind of tricky, but it's okay to sleep, and we'll sort of wake you up

when it gets to the discussion point.

These overheads are not in your book, but they will be available after the session.

I think one of the reassuring things, as I sat through the discussions and heard different parties speak about the issues here, we do actually have a common goal, and that goal is to get safe and efficacious products to patients.

The differences I think we have lie in the how to of that and when should we do clinical studies, when should we not do studies. The focus has to always be on the patient and, in particular, we should not do anything that will compromise patient safety.

We all recognize that the reasons we are having these discussions is because the complexity of biologics, protein products is such that we can't readily apply the simple approach that is used for small molecules.

We also recognize that there are many different aspects of the development program to be

considered and I think it is important to reflect on the fact that the development is really a hierarchical process and is conceptually no different when one is looking at a generic product than looking at the innovator product.

And the individual elements, whether they are analytical characterization, studying the biology, looking at immunogenicity, et cetera, those elements are complimentary to each other, but don't necessarily substitute for each other, and so you build a case throughout the development.

We have had the advantage today of hearing about yesterday's breakout sessions and also having the presentations this morning, and I think the big takeaway from all of those sessions, whether you look at analytics, biological characterization, PK/PD, immunogenicity and its determinants, it is very, very clear that there is oftentimes uncertainty around our ability to predict what will happen in the clinic.

We get a lot of good information from these methodologies, but they don't totally predict

what is likely to happen in the clinic.

The uncertainty leads to risk and the question for us is how do we minimize that risk. I think Dr. Ben-Maimon stated it correctly this morning. We can't eliminate the risk by doing clinical studies. We don't do that for innovator products. But we try to minimize that, and then, very importantly, we have risk management plans that help us manage any residual risk.

So we need to think very carefully about the risks.

The complexity of the molecule is clearly an important factor and it is the complexity, I think, that leads to the uncertainty, but there isn't just complexity about the molecule. There is complexity about the biology. There is complexity about the clinical setting. So it is the collective complexity that really drives the questions that we may have to answer in the clinical setting.

I think it is important to state that although a lot of our discussion goes toward

safety, there are concerns for efficacy and for safety, and the concerns will vary from product to product.

We know that these products are often heterogenous, they are often pleiotropic, and, again, depending on the considerations, this may lead to greater concern for efficacy or for safety.

So there really isn't a one-size-fits-all solution. I don't believe there is an algorithmic approach to how to handle these situations.

I think it is going to be rather similar to other development programs for innovative products. There is going to be a lot of case-by-case assessment that needs to be made.

So what are the clinical issues that would really drive our thinking around whether we indeed need to do studies and, therefore, what types of studies.

We heard this morning about the importance of understanding mechanism of action. Sometimes we understand that really well, sometimes less well.

What is the correlation between structure

and function? What is the structure-activity relationship? Have we well defined that? Have we defined that in something that may have pleiotropic effects?

What is the correlation between product characterization, between potency and the clinical efficacy and clinical safety? To what extent does the PK help us anticipate efficacy?

Throughout the sessions we have had in this meeting and, also, I think if you look back at the September meeting, there are plenty of examples from the innovator's experience that suggest that oftentimes these elements that we can assess are not totally predictive.

I am not going to go through those examples today, because it would take way too long, but I would encourage anyone who wasn't in the September meeting to look at the transcript. I think it is quite enlightening.

We talked yesterday about PK and limitations potentially of PK. Mark Rogge gave some good examples where the PK may be helpful or

may be a little misleading. We talked about whether pharmacodynamics will give more clarity or not.

But, again, we are still left with a sense that there is still uncertainty.

One specific issue we are all very well aware of with protein products is the issue of immunogenicity, and we had some really excellent presentations I felt this morning on the issues relating to immunogenicity. So I'm not going to cover those in any detail, but just to remind everyone, it's not only do we get immunogenicity developing, but what are the consequences; what are the consequences in a specific patient population, and those consequences can range to none at all clinically to the allergic anaphylactic type of reaction.

We may have some impact on clearance which could reduce the efficacy, or there is a very concerning case, and, coming from Amgen, I can tell you this is close to my heart, the very concerning cases with MGDF and with epoetins, where there is

quite a devastating effect on patients.

So we need to understand and anticipate that. That will guide our thinking.

We need to think about the patient population we are studying and what is the immune status of the patient. We heard this morning how interestingly with epoetins we see immunogenicity in the renal patient population.

It is not evident in the oncology population. I'm not sure we fully understand why. We could speculate as to why, but the reality is if you study it in the wrong population, you may get the wrong answer or a non-informative answer.

We need to think about issues relating to route of administration.

So this is by no means exhaustive, but it is meant to illustrate all of the complex multiple issues that we should be thinking about as we try to assess do we know enough based on analytics, biological characterization, PK/PD, or are there some uncertainties.

There may be uncertainties because we have

seen something a little bit different in the product, and that does happen with the innovator experience. We sometimes have that experience, and there we need to make a judgment based on our understanding of the molecule, based on the history of what is that likely to translate to in the clinic, and I think it was Terry Gerrard that brought that point up this morning.

We need to really understand the history of the product to make some of those assessments.

I think at the end of the day, where there is some uncertainty, whether it's uncertainty that we know or whether it's what we don't know and can't characterize, that is a situation that drives us to say we need some clinical data, because having more data will inherently reduce the risks before we go into patient treatment in a commercial world.

I am going to share with you just two examples, not in any level of detail, but give you a sense of what we deal with in the innovator world as we change processes.

We have two products where we are in the process, actually, of making substantial changes to our manufacturing process, and those are changes

impacting Aranesp and changes impacting Enbrel, and they are different process changes and I won't go into the detail, but they include major changes; for example, change of cell line.

So it's a very comparable situation that you may have with a generic product.

In the one example with Aranesp, thus far, and it's still very much in process, but thus far, from an analytic comparability point of view, the Aranesp looks identical to the product that is currently commercialized.

Nonetheless, even though we show PK bioequivalence, we plan to do substantial clinical study, partly for efficacy, but predominantly for safety. That shouldn't be a surprise. We are all very well aware of the history of epoetins and the situation with Eprex. We are very concerned about any impact that might affect patient safety.

We are also very aware that the event that

really is of interest here is PRCA and it is tremendously rare, and we shouldn't see that in clinical studies. If we did, we would have a major problem, but in all likelihood, we wouldn't see that.

But there are aspects that we can study. We can study the immunogenicity in a clinical setting. So we will be doing clinical studies that are comparable in size and duration to those for a de novo approval. So I think that shows you the extent of our concern there, and that is driven on a product change that thus far the product has been shown to be comparable.

We have another example with Enbrel, where we are undergoing some process change, and there are some rather modest changes in the product that are not all together surprising. There are some minor changes in glycosylation. There are also some changes in terms of the reduction and the amount of misfolded protein, which, at the end of the day, should be a good thing.

But because the product is not totally

comparable, we are going to do a very extensive clinical evaluation, again, comparable size studies, similar duration to studies we may have done if it was an innovator product.

So I think there are many situations, and I am sure my other industry colleagues could share similar situations that they have had, and I would encourage them to share those examples today, if they haven't already done so in the previous meetings.

So what are the factors in designing clinical studies? There is really nothing magic here. I think the key issue is what is the question. I mean, clearly, we are going to do our characterization up to the point of having clinical data and we are going to be left with some residual concern, some residual uncertainty.

So as in the case of any study, we need to have a specific objective for the study.

So these studies can be very focused and targeted and will be potentially more abbreviated or much more focused than the studies for the

innovator product. We don't need to go through proof of biologic activity. We know what we should be looking for. We understand the end points.

So we will build our study design around the specific hypotheses and study objectives we have.

There are certain methodologies. Should it be a comparator study? Obviously, if you want to be able to make a statement about comparative efficacy, then it will need to be.

Safety, I think, is a little more difficult. You can show comparison with the short-term safety, but as we have all discussed, the rare events can't be characterized in a modest sized program.

So the end points I think will be the end points that are traditionally used or maybe surrogates and I think we need to have a good robust discussion about surrogates.

The duration of the study is important, in particular, if you're looking at safety. Are you concerned about events with long latency? What is

the efficacy end point going to look like? Are we concerned about any reduction in efficacy over time if there is concern about immunogenicity and neutralizing antibodies?

The study is, again, just driven by what is the question. If we are doing a comparator study, it's non-inferiority design. What are the margins that are acceptable? I think, again, we can have some robust discussion there.

There are some specific issues I think that come up when we are discussing this topic that we need to think about. I have already raised the issue of surrogates, and maybe not just surrogates, but I also hear talk about biomarkers and I think there is maybe a not so subtle distinction between them.

So I would, again, suggest we have some good discussion around surrogates. Do we have to go with validated surrogates? We heard Jay talk about his perspective on use of surrogates for follow-on protein products.

We need to really understand can we just

study a single indication for a product that has multiple indications. Is that valid if the mechanism of action applies equally throughout? Can we do that?

What about if the effects are pleiotropic and we can't predict the efficacy, can we still study one indication or do we need to study each and every indication? So is the efficacy in one setting going to allow us to predict efficacy in another?

We know, some of the time, that will not be the case.

Is the safety predictive of safety in another setting? We heard, again, this morning, about the issues with epoetins. The PRCA events were identified in the renal population, not in the oncology population, despite quite extensive exposure.

Again, we need to look at the setting. Are we looking at chronic treatment or short-term treatment, and are we concerned about latent effects there?

The route of administration we heard particularly with immunogenicity is important. So, again, what do we study if we are going to try and

make a case for studying a single indication? Do you study worst case scenario or do you study all indications?

Then, importantly, all of this still will not be enough. It will get us to a point where there is a comfort level with approving the product, but there will still be the need to do post-approval work, whether it's just traditional pharmacovigilance or going beyond that.

So we all know that rare events cannot readily be characterized in a traditional clinical development program. That is nothing new to this setting.

So we do need to have a robust pharmacovigilance program in place to study those rare events. We need to look for events with long latency. Maybe it's a broader population than has been studied in before, particularly with generics, giving broader patient access. Maybe it's just an

exposure issue.

Immunogenicity is unpredictable and I would contend, based on everything I have heard here, that you can't predict the immunogenicity based on the innovator product. It is going to be a characteristic unique to that individual product, and then you will apply the traditional risk management approaches, spontaneous event reporting, perspective and retrospective studies, where necessary, registries, et cetera.

Again, there are no novel techniques here. The issue is what is the question at hand and what are we trying to answer.

One important point which Jay raised, I will reinforce, is that successful surveillance is dependent on accurate information, and, in particular, the reporting health care provider must know which product the patient received.

I think there is a major concern here if we look at substitution. I think you could envision a situation where, if the Eprex situation with PRCA had occurred with a generic and maybe

there was substitution and the physicians weren't aware of the product that was given, we may have never gotten a good understanding of the event and what drove that event, and that would be a tremendous disadvantage to our patients.

So I think we need to think carefully about that issue. Then at the end of the day, we need to ensure that the product label is updated with any new information, in the same way that one would do for an innovator product.

So with that, I will hand it back to David.

Thank you.

DR. ORLOFF: Thank you. I think, if I might, just before we get started with comments from the audience, I assume there will be some, to say a couple more things just by way of perhaps making the conversation more useful to everybody.

The talks we have heard this morning and then just now lay out general principles for essentially around the issues of, we'll say, levels of uncertainty about clinical safety and efficacy

of follow-on protein products.

Although I imagine that there are going to be people in this business who will take the position that you can never know what you need to know without full clinical safety and efficacy studies, if we take that position, we're not going to have a very interesting conversation.

So what we are interested in here is to discuss the details.

The first question, I am not sure we need to belabor it here, but we will take some comments on it. I would hope that we could get some, to the extent that they are out there in the audience, some specific examples of situations where clinical safety and efficacy studies are needed or would be needed based upon experience.

I think that what is going to differ in this discussion from what has gone before us in the plenary session and in the brief talks here just now will be on items number two and three here, which go to the specifics of the design of the clinical studies and the specifics of

post-marketing surveillance, which I think it is important to try to talk about since that is actually where we will probably wind up being.

So with that, let me open the floor to the audience, if there are any comments that people would like to make. Don't be shy. If you don't make them now, we'll call you back for the second session to try again.

Any comments? Here we go. The fights begin.

DR. FACKLER: Paul Fackler, with TEVA.

I guess it's an observation more than a comment. It is striking to me how similar the discussions have been today to what we heard 20 or 25 years ago with small molecule events, and I just--it struck me, in particular, as I saw the slides today, if you didn't know we were talking about proteins, you might wonder what kind of drugs we're talking about.

DR. ORLOFF: Thanks.

DR. VIVEASH: Maybe if I could just respond to that, because I have heard that comment

before and I think it is true. Clinical issues are clinical issues, whether they come up in the small molecule world or in a biologics world.

I think what is different here is the rich experience we have with actually the successful production and successful use of biologics products, but along with that success, we have learned a lot and we have had a lot of quite disturbing experiences.

Sometimes we are able to intervene before a product gets into the marketplace. Sometimes, as with Eprex, we are not.

So I think that experience should guide us, rather than some simplistic analogy to what happened and what was said in the past regarding small molecules.

There is a very rich experience here. I think the innovator industry is really willing to share that. So I think we need to listen to the experience.

DR. ORLOFF: Next?

DR. JOHNSON: Charles Johnson, Genentech.

Just to echo what Dr. Viveash said. I think one of the interesting things about the discussion which has gone on at the clinical level is the similarity of the presentations from the proponents of the two different approaches.

I think the issue that I personally have with the generic stance is that the assumption that you can well characterize the molecules that you are going to be testing, and I'm not sure, from the previous discussion that we have heard, that that is an accurate statement.

So if you claim or if you assume that we can very well characterize all of these molecules, then, yes, it may be reasonable to follow the approach that the generic chemical have taken.

But I think the whole issue is that we are not very sure that we can do that and, in the industry, as has just been mentioned, we have very clear examples of where changes in process have led to quite significant and quite potentially dangerous changes in the outcome for patients.

So I think until we understand those

things better, it would probably be premature.

Can I make one other comment?

DR. ORLOFF: And then I'm going to ask you a question.

DR. JOHNSON: Okay. Good. I think the other thing is that we are tending to lump everything together here and I think that there are, it would be fair to say, some molecules which could potentially be better characterized than others.

However, some of those molecules, for example, growth hormone, I think what one has to consider there is that the most likely populations that you would go into are those who--I have to be careful here, but shortness of stature is not necessarily a major medical problem, and the pediatric patients are an at risk population.

So I think one needs to be very, very careful in terms of gathering clinical data, even though the growth hormones may be relatively well characterized.

DR. ORLOFF: Before you leave, this gets

to the theme or the idea that I was trying to get out of this. There have been multiple examples given about where a change in process or the difference in process between one manufacturer and the next has resulted in major clinical differences related to safety or efficacy.

Is it worth considering examples in order to look at the other end of the spectrum? Is it worth considering the specifics of the examples where changes in process, different manufacturers have not resulted in appreciable changes in the safety and efficacy profile of products, despite or with the tremendous amount of clinical experience that has been garnered?

DR. JOHNSON: I think we have an example of that, to be fair. During the process of the Raptiva development for psoriasis, we transported the process from Zoma to Genentech, and did a PK study to show comparability, with fairly generous sort of bounds around that comparability, and were outside of it.

So we were there faced with a situation

where we had clearly a probably different product and we proceeded to do, I think, another thousand patient study to characterize that in the clinic. It turned out that there was no difference in terms of its effect or its safety profile.

So there are clearly occasions where there may be differences in the product, but I think it still requires that you go ahead and do those safety and clinical efficacy studies to make sure that there are not differences in those areas.

DR. ORLOFF: Let me, before you leave, then follow up with one question, which is if--I mean, it is purely hypothetical, but if the pharmacokinetic difference had not been there, are you saying that you should have and would have--forget would have--that based upon your current experience, at this point in history, you would have gone forward and still did the thousand patient trial?

DR. JOHNSON: I can assure you we would have not have done that.

DR. ORLOFF: So the difference lay in the

steps leading up to the question of do we or do we not need a clinical trial. So there is information. There are priors in the development of your product. There are priors across the history of the marketing of a given product or of a given--not class of products, because we're not talking classes.

We are talking about products that are purported to be the same, even though, at present, they are manufactured through full--they are marketed after full development programs that are individually tailored.

But in any case, I think you are telling us that there might be instances in which the priors were such that the level or the sort of critical level of clinical exposure that you needed with your drug was lowered.

DR. JOHNSON: But I should emphasize that in that situation, we transferred a process that we thought we fully understood to another manufacturing facility. We didn't change vast amounts of the process.

So I think for--

DR. ORLOFF: But you clearly don't understand that process.

DR. JOHNSON: Exactly.

DR. ORLOFF: Because you found something that didn't produce the same pharmacokinetics.

DR. JOHNSON: Right. But I think that actually is the concern, though, you would have if somebody reinvented the process without that knowledge, there would be a far greater risk that you would actually have a different product.

DR. STARK: But that is not a good example of which you could detect this uncertainty in your pharmacokinetic studies. So prior to conducting further clinical studies.

DR. ORLOFF: We don't need to go back to it. They detected a difference in the PK and that was what led them to their concern.

If they hadn't seen that difference, they wouldn't have done a thousand patients.

Could we go to my left here?

DR. SENSABAUGH: I'm Suzanne Sensabaugh.

I'm with Sicor, a subsidiary of TEVA. I would like to share some rich experience with Dawn, but not in the area of guidance documents, because I tried doing that in the immunogenicity session and it didn't work.

My company, it's no secret that we manufacture interferon alpha 2B. We have been manufacturing this product for over 15 years.

At the September meeting, we presented data demonstrating comparability of our product analytically and biologically with the brand product.

We have been distributing this product in over 17 countries and we have given over nine million doses of the product.

We manufacture the product according to CGMPs, both in the US, both in the EU. Our processes are validated. Our equipment is validated, et cetera, et cetera, et cetera.

So we manufacture in the same manner as a brand biotech product.

So I guess my question to the panel, and,

hopefully, this will enable discussion, my question would be if we do safety and efficacy trials to minimize uncertainty, what uncertainty is left to demonstrate, for this product, in a safety and efficacy trial? What is there left to look for in a safety and efficacy trial in a product in which you have been--in which you have given over nine million doses over 15 years and you know that it is comparable to the brand product analytically and biologically?

DR. ORLOFF: But with regard--I'm not understanding exactly the question. Are you saying what additional information could be needed to conclude, to render a final conclusion that your product was the same as the brand name?

DR. SENSABAUGH: I guess I'm asking, if we were to bring this product to the U.S. market, what would we need to do to demonstrate safety and efficacy? What is left for us to demonstrate?

When uncertainties in safety and efficacy are left to demonstrate in a product that has been commercially distributed for over 15 years and

which over nine million doses have been given, and you know that, analytically and biologically, it is comparable?

DR. ORLOFF: And did you say to what extent it has been studied in control and whether they are controlled with traditional controls or in well--to what extent it has been studied in well structured trials, so that where patients are carefully monitored and data are collected rigorously and all that, as opposed to relying on spontaneous post-marketing reports?

DR. SENSABAUGH: Of course, we do have a robust pharmacovigilance program.

DR. ORLOFF: Of course. But what do you have before the pharmacovigilance program? What do you have from the pre-marketing trials?

DR. SENSABAUGH: Of course, I can't share confidential information in this forum, but we do have animal and safety data that demonstrate safety and efficacy, but, of course, the trials are limited, and we did do comparability, comparing to the brand product.

DR. ORLOFF: Do people understand this question?

DR. VIVEASH: I think I understand it, but

without knowing the--

DR. ORLOFF: I need to clarify one thing. The product of which you are speaking, the very product has been given in nine million doses.

DR. SENSABAUGH: Yes.

DR. ORLOFF: The very product.

DR. SENSABAUGH: The very product.

DR. ORLOFF: But short of that experience, there is no controlled trial experience with this product?

DR. SENSABAUGH: There is limited control trial experience with this product. Yes.

DR. VIVEASH: So I think that is the crux of the matter. It is very reassuring, particularly with regard to safety, but I suspect also with regard to efficacy, that it has been given to nine million patients and you have presumably had favorable responses from the prescribers.

But I would suggest that you've got a lot

of anecdotes there that are very reassuring. The product may well be safe and efficacious, probably is reasonably safe if you've got that size of an exposure, but how do we know whether it's comparably safe and comparably effective?

Without the appropriate study data, I don't know how you could make that statement. It's not to say that the product is not safe and efficacious, but I think without the key clinical data, it would be hard to reach that conclusion.

DR. ORLOFF: Let me make a regulatory comment here. Going back to one of the presentations this morning, I believe it was Dr. Ben-Maimon's presentation, for follow-on protein products, as for follow-on small molecule drugs, we're not talking about dispensing with chemistry and manufacturing controls.

We're talking about reliance on previous findings of a reference product for assurance, on the one hand, of--not for assurance, but for sort of adopting the findings from preclinical, say, animal toxicologic findings, and potentially

clinical data with the reference product.

The question you are asking is not--well, I'm not sure it's really a follow-on protein product question, because you could, as a sponsor, you could bring forward, in some form, your nine million patient experience. Whether it would meet the FDA's standard for adequate and well controlled is open to discussion, but it's not completely out of the question.

That is to say, it is not immediately obvious that that would be dismissed out of hand. If there were some way to actually examine some of the open market experience with that product, that, in and of itself, would constitute clinical experience.

The question of whether it is the same thing clinically, so that it is substitutable, based upon an assumption or a conclusion that it has the identical or sufficiently similar safety and efficacy profile, is a completely different one, and that goes to the topic of today's question.

This product might well have--you might well have enough clinical safety and efficacy information with it to bring forward an application

that would essentially stand alone.

DR. BEN-MAIMON: I want to address that specific issue.

DR. ORLOFF: You want to address this one?

DR. BEN-MAIMON: That specific issue.

DR. ORLOFF: Please, go ahead.

DR. BEN-MAIMON: I don't want to speak for Suzanne, but I think what she was trying to say is should Sicor file an application, they have demonstrated physical and chemical--by physically and chemically characterizing their product and the reference product, the innovator product, they have shown comparability, they have been able to demonstrate that the products are comparable.

They have then done some additional work, which she, obviously, for competitive reasons, is unable to disclose, but in animals and potentially, I don't know whether they have PK or not.

Then on top of it, they have all of this

experience in all of these patients, and I think, I'm reading between the lines, but I would think that the reason for bringing that up is in response to Dawn's comments that it's experience and you have to have experience.

Clearly, Sicor has experience with this product and clearly has a robust manufacturing process and the ability to know whether changes in that process or in that product, and differences between two products will translate into clinically relevant outcomes.

So I think what she is trying to ask is given the vast experience, from a safety perspective, the comparability of the chemical itself and the data in animals or even pharmacokinetics, why would it be necessary to do any clinical trials in that circumstance for a follow-on or a generic biopharmaceutical.

DR. ORLOFF: Well, we can open that to the panel and to the rest of the audience. Does anyone on the panel want to comment further?

DR. VIVEASH: Well, I do, because it is

rather an unusual situation. I mean, if you were moving ahead now with a follow-on product of that sort, you would not, I don't think, strategically decide to market it to get nine million dose exposure.

You would typically be coming through with somewhat less than that. So it is rather a unique situation.

I think as Dr. Orloff articulated and as I tried to suggest, it may be that there is substantial data that supports safety and efficacy. It is hard for us to comment without knowing specifically what you have in the clinical context, but it still begs the question, is it comparable.

So I think there is not enough data. I mean, I think the easy way for you to find out can you file is to have a pre-filing meeting, and then you can get specific.

But I think it is almost impossible for us to answer the question you have posed without more information.

DR. STARK: I just wanted to ask what

level of uncertainties still remain with this product. What I was hearing is that there is a lot of information, both from a characterization animal model, pharmacokinetics, pharmacodynamics, and, on top of that, nine million units.

So I don't think--I really don't understand what additional information do we need to make this product available.

DR. VIVEASH: Again, I will try and restate it. Again, we've got limited information on what data you actually have in hand from the nine million units exposed.

Let's assume that there is some viable clinical data in that. I would suspect there may be a regulatory pathway to approval, but it still begs the question, so what is unknown, is it truly comparable.

So if you want it as a follow-on, I'm not sure your data will support that. It will all come down to what data do you have, and the exposure data, the clinical experience, may well be quite supported, but can you say it's comparable?

I don't know, because I don't know what data you have at hand.

DR. PETTER: Ram Petter, TEVA

Pharmaceuticals.

Dr. Viveash, you actually described very clearly the decision-making process and the risk assessment you are going through whenever you are introducing any change into a manufacturing process.

My question is actually aren't you accepting or supporting the very same concept presented by Dr. Stark?

You are talking about reducing the uncertainties. You are talking about evaluating the comparatory data.

So what exactly is different here? You gave us two examples of Aranesp and Enbrel, where you decided that uncertainties are big enough or large enough in order to drive you to conduct a full clinical study to this extent or other?

But I'm sure there were many other cases where you decided that there is no reason to do so.

So maybe there is no argument here.

DR. VIVEASH: I think on the general principles, there is a lot of common thinking. I think that is the reassuring thing about all of these discussions.

I tried to provide two examples where we did, for the reasons specified, determined that we needed to do clinical studies.

I would also, in response to Dr. Orloff's earlier question, say there are plenty of situations where we make more discreet changes and where, based on our understanding of the molecule and the history that we have at hand, the in-process controls, et cetera, that we are able to satisfy ourselves, and it does require some judgment, that there is no change.

So I think it really is a matter of integrating the data you have post-change and integrating that with the knowledge you have on the product.

I think what drives us to do the clinical studies are oftentimes the magnitude of the change.

Something that is a major change, for example, a change in cell line, I think, typically, we would want to get some clinical experience.

So a big change, regardless of whether the product looks the same or not from the analytic point of view, that was the example with Aranesp, we would still want clinical exposure, particularly in a molecule where we know products in the class have had problems.

Then the other example is one where we saw differences that, at the end of the day, may not have any clinical impact, but we can't say that with any assuredness. So we are going to do the clinical work to substantiate that.

DR. ORLOFF: So without being facetious, your answers keep coming to you, with your knowledge of your--your company, with its knowledge of its products, knows when a change or when a--when the possibility of a difference is such that clinical investigations are merited.

So how is the rest of the world supposed to know this, and, I guess, more importantly, as

FDA tries to guide industry in this endeavor, how do we know when things are problematic enough or potentially so to merit full clinical investigations?

DR. VIVEASH: I think that is a very fair question. I think, obviously, there's some intellectual property and proprietary information that is not shared in the public domain.

So the innovator, by the nature of the fact they've had a long history with a product, has access to more information.

When we are dealing with the agency, obviously, on our product, you have access to the information we have. We share that. But I realize that is a limitation for the follow-on companies, because they don't have the same access to the same rich information.

DR. ORLOFF: Well, this is not supposed to be legalities, but at some point, the agency would have to make a decision as to what would be a sufficient body of evidence to essentially permit a reliance on previous findings, because that is what

you are doing.

You are making--in the case of changing a cell line, you are making a product in a new cell line via different methodology, but your conclusion is that the two products are sufficiently similar, sufficiently similar, that you can actually go back and reference what you have known before about the product and say I can adopt this information and bring it forward to this new product, despite perhaps some differences, and other information I need to fill in the blanks.

But that is really a judgment of--at a first approximation, it is a judgment that, as far as you know, you have made the same stuff. You rendered the same basic product. There might be some details around the edges that need clarification, but you have rendered the same basic product, and, as a result, you are doing what the follow-on--you are essentially mimicking a follow-on regulatory process by relying on your own previous findings.

DR. VIVEASH: I don't disagree with what

you are saying. I think there are many parallels, and particularly in the two examples I gave. I chose them deliberately because there is parallelism.

In those situations, we are looking at a new cell line, and yet we do have the advantage of product history, not just in terms of what we saw analytically, but also what steps are critical.

So we don't usually make a wholesale change. There are some elements that are preserved and then we try to change as little as possible.

DR. ORLOFF: I'm going to make one clarifying point. By relying, what I mean is that when the follow-on company says we want to reference such-and-such a product, whether it's a small molecule or a protein product, they don't look at the preclinical animal data that are in the file for the other application.

They don't have a license to actually examine it. They simply tell us that we believe our product is similar enough based upon the following characteristics. In most instances, it

is going to be structural characterization, at least for small molecule drugs, and pharmacokinetic data.

The similarities are sufficient that you can rely on all that, but in the same fashion as you don't look back at your own preclinical data, we don't look back at those data to move forward with that new drug product.

Let me take another question.

DR. THOMAS: Adrian Thomas, Johnson & Johnson. I want to use the specific example that other people like to quote, and that is Eprex.

I was the global safety officer and I am accountable for all the divisions for our pharmaceutical sector.

The real point of interest with Eprex has nothing to do with the molecule, which speaks to why characterization is not absolutely everything, because regardless of which hypothesis you believe, what we are looking at is the effect of a very weak adjuvant, what would be the normal immunogenicity of the molecule itself.

So when you ask in what situations does clinical safety and efficacy studies offer value, I think you can look very clearly at certain products

and say, well, if not the molecule, that it wasn't adjuvant, then surely that is worthy of testing in the future, and that is our project currently within the company as to how we would evaluate any further changes that we make, is that we would absolutely be looking for signs of immunogenicity and whatever sense was reasonable.

Now, because it was a very, very weak adjuvant, clearly, a clinical safety study is not very helpful. But what's to say that there isn't a stronger adjuvant?

I think these are questions that no one really has answers to, but is a mode of thinking that we should engage in.

DR. STARK: May I comment on the issue of the Eprex? I would like to ask you a question whether these changes could have been detected by analytical methodology. Is the answer yes?

DR. THOMAS: The answer is yes, with the

new techniques we developed. However, it had nothing to do with characterization of the molecule.

It had to do with an adjuvant that was extracted by polysorbate-80 from the rubber. So to the extent that you are characterizing the epoetin alpha molecule, it's epoetin alpha and, in fact, it hadn't changed in the last 20-odd years.

But to the extent that the issue was caused by an adjuvant that had nothing to do with the molecule, yes, you could have characterized that.

DR. STARK: Another question to you is could you have detected such changes in clinical studies? According to the literature I have read, it is one of 10,000.

DR. THOMAS: The background rate that you might see with some products, including ours, might be less than .1 to one per 10,000. In the height of the PRCA episode, I will call it, the reporting rate was high as up to one in 300 in certain sites.

You have to remember this is spontaneous

reporting and reporting rates are not a very good indicator of true underlying frequency or incidence.

So, no, you would not have detected this, but as I say, this is not the only possible adjuvant that we were looking for, and the adjuvants that we were looking for were a lot more potent than this turned out to be.

So I don't think you can use this to generalize.

DR. WALTON: In the interest of time, I think we need to be careful to restrict the discussion here to the topic of this session. While the immunogenicity is very important, there is a whole other breakout session for that, and we have a number of other questions that we want to be able to work our way through.

DR. SCOTT: But I think the important point is what was brought up here is what constitutes characterization, what is the threshold that you need to meet, and you need to use the history of a product, at least problems that are

known about, to help identify how you need to characterize something.

You can't just say characterize. You really need to understand the specifics that are critical.

So I think it's a good example, even though it's immunogenicity.

DR. GARNICK: Bret Garnick, Genentech. I'll try to answer the question that was first raised about when would clinical trials be required.

I am going to echo also what Dr. Viveash said. I think one clear example of where clinical trials need to be conducted is in the case where there is a change to the cell line itself.

A new cell line, certainly, in Genentech's experience, and I presented this at the last meeting, our philosophy, of course, has been to try and not change the cell line at any point during development, including process scale-up, transfer of processes to different facilities.

Never changing the cell line is the most

important thing, because when you do, you really have changed the impurity profile of the product.

I would like to point out that a follow-on biologic, because of the legal issues, will, of course, never be produced in the same cell line as the innovator, will never use the same process, will never have, at some fundamental level, the same levels and purities, as well as product and process related impurities.

So fundamentally, we are dealing with something different and because it is a different cell line, I think there is an obligation to ensure that you look at the characterization from a biochemical, as well as PK/PD situation, as well as doing some clinical trials, and the clinical trial extent will depend on the changes, what has happened in the process, and what you are actually seeing in the characterization.

But I can assure you, and we have discussed this many times, that from our perspective, a cell line change for any of Genentech's products would also be--there also

would be a requirement, maybe not by FDA, but by the company, to ensure that, in some limited clinical trial's standpoint, we are not introducing or are about to have a surprise.

DR. ORLOFF: Before you go, the spectrum of--this kind of touches on question number two, which is what factors should be considered in design; in other words, what would be the end points of those trials.

You touched on it, but I gather what you are talking about is the possibility, again, depending upon judgment, depending upon the nature of the change and perhaps the degree of uncertainty about what the differences are in the structure and content of the product, that might go all the way from a full safety and efficacy characterization to perhaps a simple--something as simple maybe as an acute tolerability study and in between might be full immunogenicity investigations.

Is that fair?

DR. GARNICK: You said it better than I could.

DR. ORLOFF: Okay.

DR. TYAGI: Surrendera Tyagi, from Hospira. Actually, it has been kind of said

before, but it looks like we have agreement that in some cases, you always need clinical studies.

You make some changes, probably quite a few of them, where you don't need clinical studies. I assume that a number of companies go through a systematic process in the PK, the PD, and then move to the clinical in these cases when they feel necessary.

Help me understand why that is so different to do with a follow-on protein, where we will go through the same process. So in some cases, you will end up at clinical characterization and then in some cases you will move to the next level and the next level, and ultimately, in some cases, we will do the clinical study.

How is that different than what you just said, that in some cases, a lot of changes you make end up with no clinical study and, in some cases, for example, the cell line, you will do the

clinical studies?

DR. ORLOFF: I can't disagree. I don't think there is a difference in those--the consideration of those two different situations.

Harkening back to the presentations from this morning, obviously, and some stuff that has been said earlier here this afternoon, the level of understanding you have not only about the product and its structure, but also about, if you will, the specificity of its action and, frankly, the multiple steps that might characterize its action, those are two very important aspects or characteristics which essentially lay the groundwork for the extent to which you can rely on structural characterization.

DR. BEN-MAIMON: I would just like to make one comment. I think we have to make sure that we are answering the question that is being asked, which is really a regulatory requirement question.

It's not a question of whether or not a company chooses to do additional work or not. It is a question of what would the agency require in

order to demonstrate comparability.

With regard to changing cell lines, we all know that Avonex is out there. We saw the example this morning where there was a change in cell lines and the agency did approve the product based on what I think was PK and some in vitro work.

so I think we have to make sure we are answering the question, and, Dr. Viveash, I think with regard to your examples, we are in the same predicament, quite honestly. We have no data. We don't know what the comparisons are. We don't know what data you have or what your concerns or why you are concerned, and, quite honestly, we don't know whether the agency is requiring these trials or whether you are choosing to do them.

So I'm not sure that we are in any different situation than we are with whether or not to approve a product that is being manufactured in Europe with any additional data.

DR. VIVEASH: If I can just sort of respond to that general comment. All of these decisions have been made following extensive

discussion with the regulatory authorities in the U.S. and outside of the U.S., and I will also share, without giving specifics, that we hear different viewpoints, depending on who we have our discussions with.

So at the end of the day, our development program reflects the concerns and the issues that have been raised, on a scientific basis, across the globe in a regulatory environment.

So what we are doing isn't necessarily just because we believe it is correct; it is also endorsed by the regulatory authorities as being the appropriate path.

And I think vis-a-vis what question are we answering today, I think we are here because there isn't a regulatory pathway currently. So I think we were asked to focus on the science and what would drive our thinking here.

I think the regulators will actually have to come up with a regulatory answer, but hopefully taking into account the issues we raise.

DR. BEN-MAIMON: And I would just make one

other comment. The Raptiva example, I think, is actually a very important example, where the PK was discriminating and led them to do additional trial work.

And as we heard, had it not shown a difference, there would have been enough of a comfort level to bring that product to market.

So I think, again, we may all be saying the same thing, but in answer to that first question, we have a continuum and we should work with chemical and analytical characterization. If there are differences, where we still have uncertainty, we should move on to PK/PD, and if we still see differences or have uncertainty, working with the regulatory agencies and in concert with the agencies, then doing the appropriate clinical trials and not unnecessary clinical trials would be the way to proceed.

DR. FIELDER: Paul Fielder, from Genentech. I wanted to build on the Raptiva experience. Now, we did see differences in the clinic in PK/PD. What we did not pick up was

differences preclinically in either PK, PD, or biochemical characterization.

So that did go through a full preclinical characterization and it did not predict at all what we saw in the clinic.

FROM THE AUDIENCE: Maybe I can just move to a slightly different topic. I would like to hear some of the opinions from the panel and from the audience, that some of the requirements for additional clinical studies, if any, once you have established comparability, maybe in terms of the safety and efficacy or PK/PD studies, in addition to the CMC comparability was established, and then you want to go on to add another indication, which is related to the same mechanism of action.

DR. ORLOFF: Why don't you be specific about what kind of products you're talking about?

FROM THE AUDIENCE: It can be something like the insulin or the human growth hormone, which is simpler than, say, interferon or other EPO.

DR. ORLOFF: Simpler than what?

FROM THE AUDIENCE: In terms of simpler

than like the EPO.

DR. ORLOFF: So you're talking about hormones that bind specific cognate receptors with well characterized mechanisms of action.

FROM THE AUDIENCE: Yes. That's correct.

DR. ORLOFF: Does anybody on the panel want to comment? The question, I guess, is what are the conditions in which--that would require additional clinical safety and efficacy studies, not necessarily immunogenicity. You can say that word, but then you can't talk about it.

But what would be required, in what instances would clinical safety and efficacy studies, per se, be required once you had established identity based upon structure and perhaps bioassay and PK?

DR. STARK: My understanding of the question, I did understand that you are asking whether, if you have proven that the product is efficacious in one indication, should we go further to establish the efficacy in other indications that are in the labeling.

FROM THE AUDIENCE: That is correct. Yes.

DR. STARK: There were two questions, maybe. Let me try to respond.

DR. ORLOFF: Your English is better than mine.

DR. STARK: I don't know, David. Anyway, let me try to respond to that question. First of all, the underlying assumption that you have mentioned was that comparability has been shown both by analytical characterization, animal models, pharmacokinetics, pharmacodynamics, and following that, on the top of the iceberg, you have also conducted a clinical study.

You also mentioned that the mechanism of action of the product is very well elucidated and the same mechanism of action should be assured with other indications.

So in my opinion, and I am sharing only my opinion that was presented also in the September meeting, is that once you have proven that your product is efficacious in one indication, you don't need to go and duplicate and do additional clinical

studies, of course, under the underlying assumptions that we have described before.

DR. VIVEASH: I'm going to shy away from giving a specific opinion, because I don't have any direct expertise with insulins or growth hormone. I think what would be going through my mind is what is the extent of the understanding of mechanism of action; does it really translate from one indication to the other, and it may do in an environment where it is very straightforward.

In the case of insulin, I'm not sure what other indications other than diabetes you would be thinking of. Clearly, growth hormone has a broader spectrum of utility.

But I think you really have to understand does the mechanism of action really predict efficacy in all of the settings, and I think those would be the issues that would be considered.

DR. STARK: I think that we should mention the vast experience accumulated both for the innovator and during your development while we are making such a decision.

DR. ORLOFF: Can we, if I might, turn the discussion to the last item, because it seems that is the one we really haven't discussed, and that is

the issue of post-marketing surveillance as part of risk management.

If we could move to that topic, I would appreciate it. This is something that has been tossed about in a lot of the presentations I have heard this morning and yesterday morning, I wasn't here yesterday afternoon, and it falls easily off of people's tongues, risk management and post-marketing surveillance.

But we have heard a couple of examples about the need for assurance in post-marketing of what product within the range of presumed similar marketed products a patient is using in order to infer or to make inferences with regard to role of the drug or role of the specific agent in some adverse event that is observed post-marketing, and that is not, I think, a simple thing to ensure in post-marketing.

So if people have some thoughts about how

this should be approached and some generalities, as well as some specifics would be helpful.

DR. THOMAS: We've had a lot of experience with post-marketing surveillance with biologics, particularly related to the issue at hand that we had, and I guess we conducted them in a couple of different senses.

One is where you know exactly what you're looking for and you stimulate reporting, you capture a population and are able to look for some reliable surrogates.

For example, for PRCA, we're not interested in anything really other than an antibody positivity or surrogate for that, which might be secondary loss of effect.

In general, though, I think post-marketing surveillance is highly useful for rare adverse events, but only when you know what you're looking for and when you're confident that the population you are examining has a good reporting rate.

In general, the good news for biologics is that they tend to be used by a highly specialized

group of physicians who understand the importance of adverse event reporting, and where you do have an issue that is identified, then you can target and then hone on those.

But I agree, I find the words risk management plans and post-marketing plans do roll off at the end of a statement about marketing products as if that is supposed to give reassurance to everyone, but I think without very careful attention to the design and the targets that you are looking for, that can be more or less meaningless.

DR. ORLOFF: Before you leave. For erythropoietin products, for example, are those products, to your knowledge, or anyone else here, are they all marketed under actual regulatory commitments to enroll patients in registries, either mandatorily or voluntarily? How do we know that a substantial number of people who are getting erythropoietin products are getting recorded and particularly that their chart doesn't just say EPO, X amount per period, but exactly what the product

was that they got?

DR. THOMAS: You ask a really good question. I guess from our company's perspective, we have a voluntarily agreed surveillance program for our product, but one of the things we found when we dug into hospital practices globally is that someone could want Eprex and they might very well get another product next month because the hospital changed to a lower priced product.

And when you try and get down into what product they actually received, you need to get into the level of information around a pharmacy record or patient case record, which has all sorts of privacy issues and is quite hard to do.

So I think the question comes, if you have enough concern, then you would mandate a registry in order to track the product, but that is actually very hard to track products and get to a level of certainty about what was actually used.

DR. ORLOFF: Well, it is important to point out, from what I understand of the law, that imposing the things like registries or maintenance

of registries on follow-on manufacturers is not--I don't think it is allowed for directly in our system currently. So it does pose a problem.

Do you want to comment and correct me on that? Go ahead.

DR. JOHNSON: Charles Johnson, again, Genentech. I wasn't going to correct you, but I would just provide the perspective that our company has been quite aggressive about, with the assistance of the FDA, obviously, about conducting formal post-marketing registries, and I think particularly on the growth hormone front, where a large number of companies have conducted those registries, prospectively collecting information on patients who get specific products, that actually gives us the level of confidence that we have about the safety of those products.

I think that from our point of view, we would expect to be doing that with all of our innovator products, and I think that that prospective collection of specific pieces of information gives you a far better post-marketing

surveillance.

DR. ORLOFF: Before you sit down, because you might want to address this. So this question, what concerns can be addressed or why don't we say what concerns should be addressed, I mean, we could take the position that any follow-on protein product or any protein product, for that matter, because they are complex, because you can never quite know everything and you never can quite know as much about them as you know about small molecule drugs, that all of them should be followed with directed post-marketing surveillance.

That is to say, proactive as opposed to--active as opposed to passive. But maybe that's a little too drastic.

What are the specific instances in which we would want to impose those registries?

Let me just clarify for people that it is my understanding that the basis for the growth hormone registries had nothing to do with the concern of, say, reactions to impurities in growth hormone products. It had to do with the fact that

it was unknown at the time when the use of growth hormone was anticipated to explode with the introduction of recombinants, it was unknown really what might be the length and breadth of adverse growth promoting consequences of chronic growth hormone administration.

So that is something a little different than what actually we are talking about here for most of the time.

So thoughts.

DR. JOHNSON: I absolutely agree with you and I think, obviously, the two things that people were concerned about were the promotion of leukemia in these small children, which the registries were able to show was not as much of a concern as had been thought, theoretically, and I think, also, the recent reports that we have seen from some of the long-term follow-up of the human-derived growth hormones in terms of the oncology adverse events.

Because of the long-term follow-up that we have been able to have, we have been able to analyze our data with the recombinant human

proteins and show that. So that there are advantages of having these registries to evaluate things which crop up that you didn't know about.

So to quote Mr. Rumsfeld just down the road, one of the advantages are that you may pick up the things that you don't know that you don't know.

But I think that there are huge advantages and particularly when the issues around biologics related to adverse events may be infrequent, it does suggest that the formal collection of prospective data has some place potentially.

DR. ORLOFF: So I think the answer you gave me is that you might actually need it for every single biologic product.

MS. MUNKER: My name is Christine Munker, with Barr Laboratories.

I just wanted to address the risk management issue. Risk management is not new to the generic industry. We participate in a number of risk management programs, formal risk management programs through the agency.

We abide by the risk management guidance that is out there, and we have a number of products based on the product itself, whether it's an

HIV-AIDS product, where there are pregnancy registries.

So it is something that we are actually very comfortable in working with the innovator companies and participating on these programs and sharing the data.

So it is something that I have to say is not new to us and we have actually--products such as clozapine, isotretinoin in the HIV. So it is something we are very comfortable with and we understand the risks and the benefits associated with these products.

MS. YAMASHITA: Elizabeth Yamashita, Bristol-Myers Squibb. There's been a lot of parallels to the innovator development program and the way that follow-on proteins might be developed and registered.

I would just mention that for accelerated review of, say, an oncology product, you get in a

little bit faster, limited data, and you usually will end up with some kind of post-surveillance commitment. I don't see any difference in this approach.

In some respects where you might have even less clinical data, it make sit that much more important to be tracking the product for some period of time after it's into the open market.

DR. ORLOFF: So I think what you are asking is, if I might translate to our purposes here, which is to the extent that post-marketing surveillance is intended to provide evidence that you don't--you may not necessarily be able to get pre-marketing.

At least typically, post-marketing surveillance assumes that there is something sinister that might accrue once it goes out into the huge numbers to whom a drug is administered in post-marketing.

So are there instances--so I guess the question is how do you balance the need for preapproval information, clinical information,

before you go forward against the possibility that maybe you might address some of these unknowables, but where you had reasonable assurance of safety and efficacy, and how would you address some of these unknowables in post-marketing.

Does anybody have any comments on what specific situations you might want to say err on the side of relying on post-marketing or situations in which you wouldn't dare go forward unless you had full clinical and safety before you approved?

MS. YAMASHITA: Can I just add?

DR. ORLOFF: Yes, please.

MS. YAMASHITA: I would say that regardless of whether you do clinical studies on follow-on proteins before it is registered or not, because of the very limited clinical experience, it makes a lot of scientific sense to make sure that you have a strong surveillance program put in place for a specific period of time.

DR. ORLOFF: Alison.

MS. LAWTON: Just to follow-on on the previous comment. I do want to point out what I

think is a significant difference between accelerated approval and post-market surveillance versus a follow-on in post-market surveillance, and that is the risk-benefit ratio.

For many, if not all of accelerated approval products, they reason that they are given accelerated approval is because there are no other therapies, there is no other choice for patients.

So the benefit far outweighs the risks. I think that is a very different situation when we are talking about a follow-on protein where there is already a therapy available.

So I just wanted to comment on that.

DR. ORLOFF: Thank you.

DR. PETTER: Ram Petter, TEVA Pharmaceuticals. Just a comment on the last remark we heard.

Actually, for many Americans and many more human beings elsewhere, there is no alternative. So the generic affordable medicine is the real alternative for them and there is no reason to put any unnecessary obstacles in the way of approval of

these compounds.

DR. ORLOFF: Thank you. Any other comments?

DR. SCOTT: I could say, from my point of view, at any rate, it has been a very good discussion and if anybody sees something that I have written that they think is incorrectly stated, please let me know after the session.

It seems to me, though, that there was a comment made that these--what the innovator does and what the follow-on group does are very largely the same and the concerns are very largely the same, but what I see is that the actual threshold for the clinical study requirement is still somewhat different.

I would also like to point out that with the innovator, even when there are major manufacturing changes, there's still a lot of manufacturing that remains the same and one feels that it is, in a sense, still more well characterized with respect to the manufacturing change and if you compare that manufacturing method

to the innovator's manufacturing method.

DR. ORLOFF: Okay. Why don't we break? Thank you, everybody, for your comments.

[Whereupon, the session recessed, to resume in another session, that same day.]

- - -